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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,545	04/05/2006	Enrico Anthony Antonini	1679 WO/US	4059
Jeffrey S Boone Mallinckrodt Inc 675 McDonnell Boulevard PO Box 5840 St Louis, MO 63134				
7590 03/12/2009				
EXAMINER				
CHANDRAKUMAR, NIZAL S				
ART UNIT		PAPER NUMBER		
1625				
MAIL DATE		DELIVERY MODE		
03/12/2009		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/574,545

**Applicant(s)**

ANTONINI, ENRICO ANTHONY

**Examiner**

NIZAL S. CHANDRAKUMAR

**Art Unit**

1625

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 16 February 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1 and 3-25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)
- Paper No(s)/Mail Date \_\_\_\_\_

- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

Applicants Response filed 02/16/2009 is acknowledged.

Claims 1, 3-25 are pending.

**Response to Applicants Remarks**

Applicants Remarks center on

1. Obviousness Rejection over US 4317903
2. General Remarks Relating to Additional Prior Art References
3. Declaration of the Inventor
4. Failure to consider the Patentability of Dependent Claims
5. Double Patenting Rejection

**Response:**

**1. Obviousness Rejection over US 4317903**

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Previously presented rejection of claims 1, 3-25 as being obvious over the teachings of Hofstetter US 4317903 is maintained for reasons of record. Applicant's arguments were fully considered but are not persuasive.

Applicant state that the claimed subject matter of process of purification of fentanyl sample containing fentanyl and phenethyl piperaniline is in contrast to the claimed subject matter of Hofstetter. Applicant further states that the Examiner did not establish that the difference is mere substitution of one known element for another known element.

Specifically Applicant states that Fentanyl and Lincomycin are not interchangeable because of the various structural factors. Examiner disagrees. What is at issue is the 'process of purification'. The compounds and the impurities are of course structurally different. Fentanyl and Lincomycin are polar amines. Normal phase chromatographic purification of polar amine molecules over silica gel is known in the art to cause problems such as trailing and spreading of the already tightly bound (because of the acid silica gel and base amine interaction) amine requiring large elution volumes. The predominant factor for the choice of reverse phase liquid chromatography in the case of Fentanyl and Lincomycin is based on the presence of the basic amine structure. The analogy is limited to this. As such the arguments based on differences in functional groups and structural differences present in the two compounds are thus not pertinent to the instant invention of hplc process, and thus applicant's arguments are not persuasive.

Secondly, applicant argues on the basis of the limitation phenethylpiperaniline. This argument is not persuasive because the issue at hand is the process of purification of organic compounds by the hplc methods. The presence of the impurity phenethylpiperaniline is due to the many processes for synthesizing Fentanyl using 1-(2-phenethyl)-4-anilinopiperidine based on Jonczyk, et al. Przemysl Chemiczny 1978, 57, 4, 180-182. It is well known that most, if not, all organic reactions result in some impurity or unreacted starting material (as in the instant case 'phenethylpiperaniline'). Organic chemist use chromatographic methods as one of many routine laboratory practices for the purification of the desired products of organic reactions. It is the Examiner's position that, as stated earlier, the Hofstetter reference is one example of hplc purification methods commonly employed in the organic chemistry laboratories (See New Rejections). As such the recitation of solvents, loading ratio, or % impurity does not make a commonly used laboratory technique unobvious.

## **2. General Remarks Relating to Additional Prior Art References**

Applicants argue that they are not required to respond to Examiners General Remarks relating to Additional Prior Art References. Applicant states that references in minor capacity should be positively included in the statement of the rejection. Response: 'Prior art not relied upon' was the section title for the cited references and these references were not included in the rejection.

Further applicant objects to the 'Editorial Review' found on GOOGLE in the introduction to HPLC: Practical and Industrial Applications by Joel Swadesh.

This was cited in response to applicant's arguments to previously made rejection to indicate the Text Book teachings of the state of the art of hplc as a routine method for purification of organic chemicals. The objection is acknowledged.

### **3. Declaration of the Inventor**

Applicant state that the Examiner failed to fully consider the declaration of Enrico Anthony Antonini. Examiner disagrees. Examiner did consider the declaration filed 09/25/2008 and indicated so in the previous office action. Further, applicant states that the Office must specifically explain why the evidence is insufficient.

The substantive items 3, 4, 5, 6, 7 are reiteration of what are already present in the instant specification and in the disclosure of Hofstetter reference. These items also state the fundamentals of general state of the art of analytical and preparative chromatography. Items 1,2 are factual. Items 8, 9 are conclusionary but also see the obviousness rejections. As such, the affidavit does not lend support as to the non-obviousness of the instant process.

On page 8, applicant states that the Rejection is based on a single reference and if the Examiner wishes to make further rejections, applicant requests that those rejections be made of record. Examiner agrees. See section titled New Rejection.

### **4. Failure to consider the Patentability of Dependent Claims**

Applicants state that the Examiner failed to address the patentability of dependent claims and limitations recited therein. Examiner disagrees. All the

limitations were considered. The claims, for example claim 25, recite routine practices in the methods of hplc. For example, in claim 25 (pointed out in the applicants remarks), the steps refer to discarding a first cut and to combining, concentrating and recycling; the third step is a statement of what was observed.

One of ordinary skill in the art would understand such limitation as to discard a fraction of eluate if the fraction does not contain any useful material, or recycle fractions that contain desired material contaminated with undesired material. The determination of loading ratios, collection of various fractions (cuts), combining the fractions containing similar compositions of the desired products or impurity and recycling are all part of any chromatographic method and thus well known to one skilled laboratory technician.

## **5. Double Patenting Rejection**

Examiner agrees with the Applicant to hold the double patenting rejection in abeyance.

### **New Rejections:**

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, claims 3-23 (which depend on claim 1), claims 24 and 25 rejected under 35 U.S.C. 103(a) as being unpatentable over the teaching of HPLC methods taught, independently, in Abbot et al. US 4234684, Debono et al. .US 4293489, Hamill et al. US 4336333, Fukuda et al. US 4904590 as well as Lazarus et al. US 5780589.

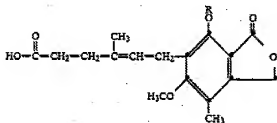
#### **Instant Claims**

The instant claim 1, claims 3-23 (which depend on claim 1), claims 24 and 25 are drawn to an industrial process for the purification of fentanyl using reverse phase high performance liquid chromatography (hplc). The various claims include limitations of the impurity in the sample of the impure fentanyl preparation, various stationary silanized silicagel solid supports, mobile phases, doping acids, and operating pH etc. These claim limitations refer to routine operating procedures of column packing, selecting solvents, determining loading ratio, collecting, combining and recycling etc, protocols well known in the art of organic laboratory practice.

#### **Prior Art**



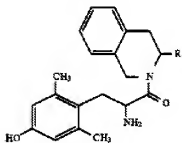
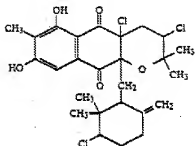
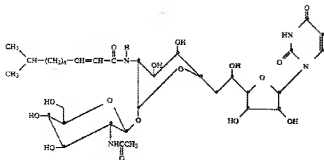
Abbot et al. US 4234684 Column 9 and 10, teach hplc purification of glucoside of



- 1 R=H (mycophenolic acid);  
2 R= $\beta$ -D-glucopyranosyl (mycophenolic acid glucoside).

[illegible]

Hamill et al. US 4336333 Column 13 and 14 teach hplc purification of Tunicamycin



whether the first cut is discarded or whether the second cut is combined with a fourth cut or not.

One skilled in the art of process research developing processes for purification of commercially important fentanyl would be motivated to use hplc methods by routine optimization of various commonly used hplc parameters such as solvent, solid support etc. for purification of fentanyl because prior art teaches the conditions necessary of purification of a variety of polar molecules by optimization of hplc procedures. .For example, substituting impure fentanyl for Tunicamycin or mycophenolic acid glycoside as taught in the cited references would require routine optimization of parameters such as loading ratio, elution rate, elution volume etc. but these would be within the capabilities of one skilled in the art of purification technology. MPEP states that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claims 1, 3-25 are not allowable.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/  
Primary Examiner, Art Unit 1625

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